Brief Review

NADPH Oxidase-2 and Atherothrombosis
Insight From Chronic Granulomatous Disease

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Abstract—The phagocytic cell enzyme NADPH oxidase-2 (Nox2) is critical for killing micro-organisms via production of reactive oxygen species and thus is a key element of the innate immune system. Nox2 is also detectable in endothelial cells and platelets where it has vasoconstrictive and aggregating properties, respectively. Patients with X-linked chronic granulomatous disease with hereditary Nox2 deficiency not only have impaired bacterial killing but, in association with loss of Nox2 function, also have enhanced carotid artery dilation, impaired platelet-related thrombosis, and reduced carotid atherosclerotic burden. Experimental studies corroborated these reports in chronic granulomatous disease by demonstrating (1) Nox2 is upregulated in atherosclerotic plaque, and this upregulation significantly correlates with oxidative stress and (2) pharmacological inhibition of Nox2 is associated with a delayed atherosclerotic progression in animal models. Furthermore, the role of Nox2 in platelet-associated thrombosis was substantiated by experiments showing impaired platelet activation in animals treated with a Nox2 inhibitor or impaired platelet aggregation along with reduced platelet-related thrombosis in the mouse knockout model of Nox2. Interestingly, in chronic granulomatous disease patients and in the mouse knockout model of Nox2, no defects of primary hemostasis were detected. This review analyses experimental and clinical data suggesting Nox2 is a potential target for counteracting the atherothrombotic process. (*Arterioscler Thromb Vasc Biol*. 2017;37:00-00. DOI: 10.1161/ATVBAHA.116.308351.)

Key Words: atherosclerosis ■ eicosanoids ■ foam cells ■ monocytes ■ oxidative stress

Atherothrombosis encompasses a sequence of events whose hallmarks are atherosclerotic plaque formation and the ensuing thrombotic complications at sites of plaque rupture or erosion.[1] Key steps in the atherosclerosis process include accumulation and oxidation of low-density lipoproteins (LDLs) by reactive oxygen species (ROS) within the artery wall and perpetuation of the inflammatory process via infiltration of monocyte–macrophages, which become foam cells on uptake of oxidized LDL.[1] The atherosclerosis process eventually can result in rupture or erosion of the arterial wall with subsequent platelet aggregation locally and thrombus formation, known as atherothrombosis, resulting in occlusion of blood flow and downstream cellular damage. ROS are implicated in the process of atherothrombosis with other mechanisms including arterial dysfunction via NO inactivation or NO synthase inhibition and platelet activation via overexpression of platelet eicosanoids and platelet NO inhibition.[2]

Among the enzymatic pathways involved in ROS formation, NADPH oxidase (Nox) is among the most important cellular producers of ROS.[3] The Nox family includes several isoforms including the phagocytic Nox2, which is a key component of the innate immune system because it greatly contributes to bacterial killing.[4] Nox2 is a transmembrane protein whose gp91phox and gp22phox subunits form a membrane-bound heterodimeric flavocytochrome b558, which acts as a catalytic core. Nox2 was originally identified in phagocytes, but subsequent studies demonstrated that it is also expressed in endothelial cells, cardiomyocytes, hematopoietic stem cells, and platelets.[3] Activation of Nox2 requires translocation of cytosolic subunits, namely, p47phox, p67phox, p40phox, and Rac1 to the membrane flavocytochrome b558 complex comprising gp91phox and p22phox3. Once assembled, Nox2 activation results in electron reduction of oxygen to superoxide anion $O_2^{\cdot-}$), which rapidly dismutes to hydrogen peroxide and then is converted by neutrophil myeloperoxidase to hypochlorous acid (bleach) and then to chlorine. These products are all potent antimicrobial agents.[5] In other cells, ROS exert different activities.[3] For example, $O_2^{\cdot-}$ can rapidly react with and inactivate NO thereby impairing its vasodilating property and hydrogen peroxide, reportedly possesses vasodilating and platelet aggregating properties.[6]

Patients with the clinical syndrome resulting from loss of function of Nox2, chronic granulomatous disease (CGD), have increased propensity to infection with certain bacteria.[4] CGD is caused by mutations in any of the 4 genes encoding subunits for superoxide anion generation.[4] Approximately 60% CGD patients have hereditary deficiency of the Nox2 subunit glycoprotein gp91phox (X-linked CGD), ≈30% have autosomal recessive hereditary deficiency of the Nox2 subunit p47phox, and most of the remainder of patients have autosomal

Nonstandard Abbreviations and Acronyms	
CGD	chronic granulomatous disease
FMD	flow-mediated dilatation
LDL	low-density lipoprotein
Nox	NADPH oxidase
$O_2^{\cdot-}$	superoxide anion
ROS	reactive oxygen species

recessive deficiency of the Nox2 subunits p67[phox] and p22[phox]. Although X-linked CGD is complicated by life-threatening infections consequent to severe impairment of ROS formation,[4] hereditary deficiency of p47[phox] displays less marked reduction of ROS production, milder infectious disease, and longer survival.[7] Importantly, investigation of X-linked CGD patients have provided a clinical model that can be used to test the hypothesis derived from observations in these patients and from experiments with mouse knockouts lacking Nox2, suggesting a role for the phagocytic Nox2 in the atherothrombosis and its clinical sequelae.[8–12] Here, we review the experimental and clinical studies that explored the relationship among Nox2, atherosclerosis, and thrombosis in both humans and mice. The published data suggest that Nox2 represents a novel target for developing drugs to potentially prevent and treat atherosclerosis and its vascular complications.

Nox2 and Atherosclerosis: Experimental and Clinical Studies

Studies in knockout animals lacking either Nox1 and Nox2 have suggested that these isoforms modulate artery vasodilation by interfering with NO bioavailability.[13,14] These findings have been reinforced by investigating 3 patients with X-linked CGD flow-mediated dilatation (FMD), which is an ischemia–reperfusion model dependent on endothelial release of NO.[15] We speculated that in Nox2 deficiency, impaired inactivation of NO would result in enhanced NO bioavailability and arterial dilatation. Consistent with this hypothesis, FMD was enhanced in the 3 X-linked CGD and blunted by IV injection of L-NAME, an inhibitor of NO synthase.[15]

The results of this FMD pilot study were corroborated by a multicenter trial in CGD patients. Compared with controls, FMD was significantly increased in CGD patients with gp91[phox] or p47[phox] deficiency,[8,16] with a more marked artery vasodilation in patients with gp91[phox] deficiency.[16] The relationship between Nox2 and artery dilation was confirmed in another model of ischemia–reperfusion, which is characterized by impaired artery dilation on 20-minute ischemia of upper limb followed by reperfusion[17]; this phenomenon was not observed in patients with CGD.[17]

Relevant to the vasoconstrictive effect of Nox2 was the significant reduction of urinary excretion of 8-iso-PGF2α and the increased serum nitrite/nitrate in CGD patients, suggesting that Nox2 is implicated in 8-iso-PGF2α production and NO downregulation.[8,15] Thus, there are at least 2 mechanisms potentially contributing to Nox2-dependent artery vasoconstriction, one being related to impaired NO biosynthesis and activity and the other to overproduction of 8-iso-PGF2α,

which is present in human atherosclerotic plaque and might be vasoconstrictive[3] (Figure 1). Further study is, however, necessary to assess how oxidant species orchestrate artery motility because other vascular Nox isoforms have opposite effects. Thus, the vascular wall contains several Nox isoforms, such as Nox1, Nox4, and Nox5, which may influence arterial motility.[18] Nox4 produces H_2O_2, which has a vasodilating effect via eNOS activation,[19] and animal studies showed that genetic deletion of Nox4, unlike Nox2 deletion, leads to endothelial dysfunction and increased atherosclerosis burden.[20]

An interesting finding of the CGD study was the significant reduction of carotid intima–media thickness,[8] which is a surrogate marker of atherosclerosis, as detected by Doppler ultrasonography[21]; this finding was observed in children[8] and later confirmed in an adult cohort of female carriers of gp91[phox] deficiency.[22] Using a more sophisticated diagnostic approach, that is, magnetic resonance imaging and computed tomography, Sibley et al[10] extended these preliminary reports by demonstrating that adult CGD patients, compared with age- and sex-matched healthy control subjects, had a 22% lower internal carotid artery wall volume with a similar reduction detected in both p47[phox]- and gp91[phox]-deficient subtypes.[10] In contrast, the prevalence of coronary arterial calcification was similar between patients with CGD and controls. In another clinical study of CGD patients, Leiding et al[23] reported that p47phox-deficient patients, whose phagocytes make a small amount of residual ROS, have more cardiovascular disease than patients with gp91phox deficiency in whom impaired ROS production is more severe.

Analysis of the activity and expression of Nox2 in human atherosclerotic plaque consistently demonstrated an upregulation of the enzyme or its subunits in the atheroma from carotid and coronary arteries. In an experimental model of carotid lesion induced by flow cessation, Khatri et al[24] demonstrated that, in transgenic mice overexpressing the Nox subunit p22[phox], progression of carotid artery lesions was more marked compared with lesions in wild-type mice; this effect was mitigated by the antioxidant ebselen. In coronary sections from human autopsy cases Azumi et al[25] showed that in nonatherosclerotic coronary arteries, p22[phox] was also expressed but weakly and mainly in the adventitia. Conversely, in atherosclerotic coronary arteries, p22[phox] was overexpressed in the neointimal and medial smooth cells and in infiltrating macrophages in hypercellular regions at the border of atheromatous plaques.[25] Furthermore, Guzik et al[26] showed enhanced superoxide production in coronary arteries from patients with coronary heart disease in association with upregulation of p22[phox] and gp91[phox], suggesting that both these subunits contribute to oxidative stress in human coronary atherosclerotic lesions.[26]

Further evidence for an association between Nox2 activity and atherosclerotic progression was established in experimental knockout mouse models of gp91[phox] deficiency and ApoE, which predisposes to atheroslerosis. Judkins et al[11] developed a double knockout, generating genetically related strains of gp91[phox−/y]/ApoE^{−/−} mice compared vascular ROS production, NO bioavailability, and atherosclerotic plaque formation along the ascending and descending segments of the aorta in the ApoE^{−/−} single-knockout mice and in gp91[phox−/y]/
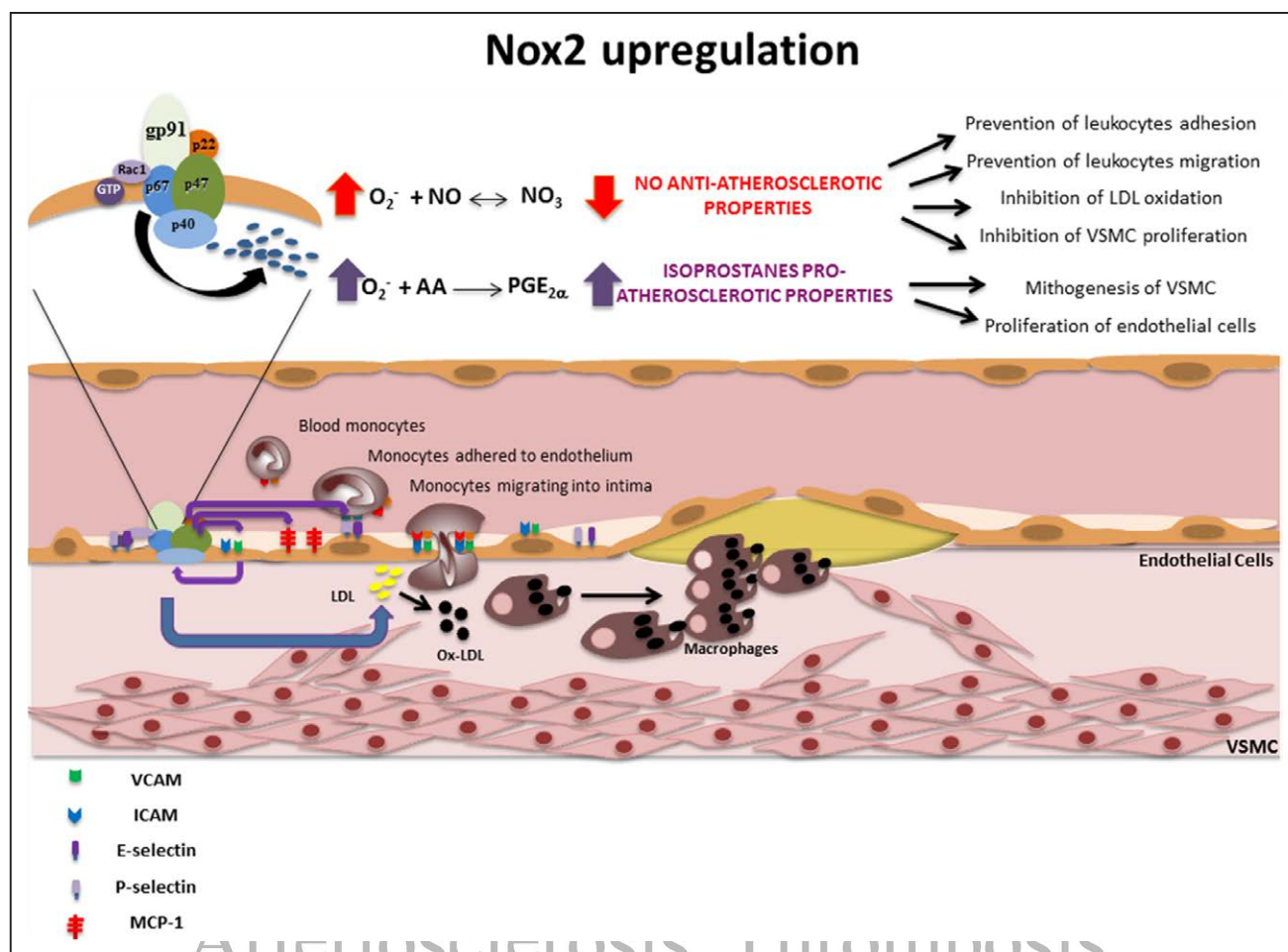
Figure 1. Role of NADPH oxidase-2 (Nox2) in the atherosclerotic process. Nox2 is expressed in the artery wall where, if upregulated, can elicit vasoconstriction via inhibition of NO activity and biosynthesis. Moreover, Nox2 activity can induce adhesion and chemoattractant molecule upregulation, NO downregulation, and isoprostane overproduction, which contribute to artery wall inflammation and eventually atherosclerosis. AA indicates arachidonic acid; ICAM, intercellular adhesion molecule; LDL, low-density lipoprotein; MCP-1, ; Ox-LDL, oxidized low-density lipoprotein; O_2^-, superoxide anion; VCAM, vascular cell adhesion molecule; and VSMC, .

ApoE$^{-/-}$ double knockout. gp91$^{phox-/y}$/ApoE$^{-/-}$ mice disclosed a profound reduction in superoxide production, a significant improvement in NO bioavailability, and markedly less atherosclerotic plaque burden along the length of the aorta compared with ApoE$^{-/-}$ mice.[11] Of note, this experimental model was not associated to any change in atherosclerotic lesion of the aortic sinus, which is consistent with a previous similar study by Kirk et al,[27] suggesting that Nox2 might not be involved in the atherosclerotic process of this specific area. The relationship between Nox2 and atherosclerosis was also evidenced by investigating the mouse knockout for the cytosolic Nox2 subunit p47^{phox}. These animals displayed less adventitia fibroblast proliferation and reduced atherosclerotic lesions.[28,29] However, in another publication crossing p47phox deficient mice with ApoE$^{-/-}$ mice, Hsich et al[30] reported no effect preventing the progression of atherosclerosis although in this experimental model the superoxide reduction in the p47phox-deficient mice was only 50%.

Pharmacological interventions with Nox2 inhibitors also support a role for Nox2 in the atherosclerotic process. In ApoE$^{-/-}$ mice treated with Nox2ds-tat, which binds to the p47^{phox} subunit and prevents its interaction with the core

membrane-integrated cytochrome b558 protein, Quesada et al[31] demonstrated delayed progression of the atheromatous plaques and inhibition of vascularization, thus reversing vascular pathology arising with atherosclerosis. Furthermore, in mice deficient for both LDL receptors and Apobec-1, Liu et al[32] demonstrated that apocynin, a molecule that impairs p47^{phox} translocation to the membrane subunit Nox2, dose dependently lowered total monocyte plaque accumulation, platelet adhesion, and atherosclerotic progression.[31] In the same publications, animals prone to atherosclerosis were also characterized as having impaired artery elasticity, which was reversed by apocynin treatment.[32]

There are still several open issues about the role of Nox2 in atherosclerosis. Nox2 is expressed by vascular cell subtypes such as endothelial cells, smooth muscle cells, and adventitia,[33] but it remains to be clarified whether activation of Nox2 by specific vascular sources is implicated in atherosclerosis. For instance, adventitial cells are an important source of Nox2-derived superoxide anion formation, which may have a role in the atherosclerotic process as suggested by more pronounced immunoreactivity of p22phox in the adventitia of human atherosclerotic coronary arteries compared with
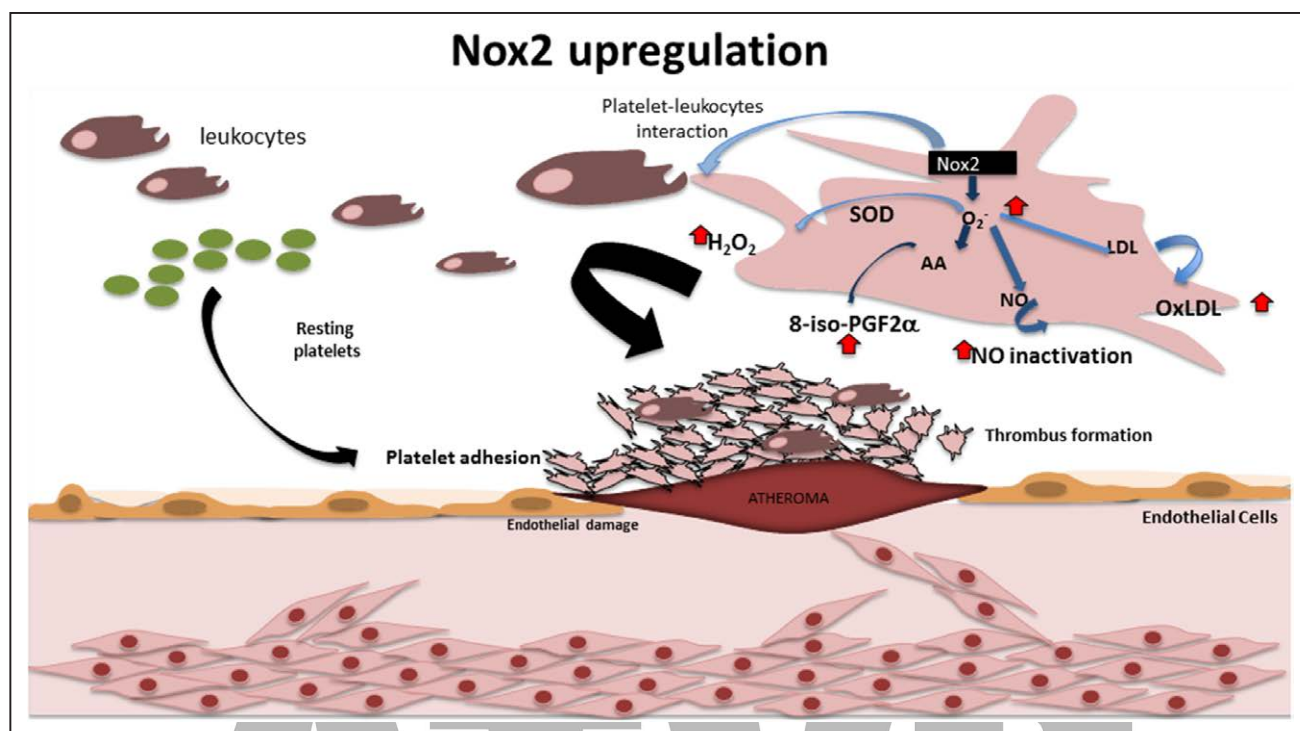
Figure 2. Role of NADPH oxidase-2 (Nox2) in the thrombotic process. Nox2 is expressed on platelets, where, if upregulated, facilitates platelet aggregation via formation of oxidant species, such as H_2O_2, 8-iso-PGF2α, and ox-LDL, or NO inactivation and then induces platelet–leukocyte interaction. AA indicates arachidonic acid; LDL, low-density lipoprotein; Ox-LDL, oxidized low-density lipoprotein; $O_2^{.-}$, superoxide anion; and SOD, .

nonatherosclerotic ones.[25,33] However, data about a role for vascular smooth muscle and adventitial cell Nox2 expression and atherosclerosis are still undefined; conversely, 1 experimental study demonstrated that upregulation of endothelial Nox2 favors endothelial dysfunction and atherosclerosis.[34] Thus, in mice overexpressing endothelial Nox2, an early increase of endothelial activation and macrophage accumulation within the subendothelium layer were detected compared with controls, whereas no difference in either atherosclerotic plaque area or in plaque progression was detected in aged animals.[35]

Prospective studies should investigate the impact of Nox2 deficiency on human atherosclerosis progression. This would be particularly useful in view of the fact that chronic infection and inflammation associated with CGD could counteract the antiatherosclerotic effects in Nox2 deficiency. However, in adults with complete or partial deletion of Nox2 CGD carotid thickness, as assessed by magnetic resonance imaging or Eco-Doppler ultrasound, was significantly reduced independently from the coexistence of atherosclerotic risk factors or systemic inflammation.[10,22] The disassociation of loss of Nox2 function and increased atherosclerosis risk suggests that loss of Nox2 function prevents or retards atherosclerosis progression even in a disease such as CGD. Experimental and clinical studies of p22phox polymorphism also support this hypothesis. For example, C242T single-nucleotide polymorphism causes changes of p22phox, which results in impaired Nox2 activation and reduced endothelial oxidative stress[36,37] and, in coronary heart disease patients, is associated with a lower recurrence of cardiovascular events compared with homozygous carriers of C allele.[38]

Delineation of the exact mechanism by which Nox2 relates to atherosclerosis requires further investigation. In addition to eliciting artery dysfunction via oxidative stress induced by ROS products, Nox2-derived oxidative stress may also activate mechanisms that are suggested to play a role in the atherosclerotic process. For example, endothelial activation, monocyte migration into the vessel wall, and vascular smooth muscle cell proliferation are all important in the pathogenesis of atherosclerosis (Figure 1). Nox2-derived oxidative stress may, in fact, elicit expression of adhesion molecules, such as vascular cell adhesion molecule, intercellular adhesion molecule, and E-selectin, and the chemoattractant MPC1, which promote monocyte adhesion, migration, and accumulation in the subendothelium[33] (Figure 1). Of interest is the interplay between Nox2 and adhesive molecules in mice lacking the Nox2 cytoplasmic subunit p47phox. In these p47phox knockout mice, tumor necrosis factor-α failed to induce expression of intercellular adhesion molecule-1 in coronary microvascular endothelial cells.[39] In other studies both in animal and human models, ROS elicit expression of vascular cell adhesion molecule-1, which serves as a scaffold for leukocyte migration and a trigger for endothelial signaling via inducing Nox2 activation.[40]

Nox2-derived oxidative stress may also promote atherosclerosis via NO downregulation and isoprostane overexpression. NO downregulation is relevant for the atherosclerotic process as demonstrated in mouse models where it prevents leukocyte adhesion to vascular endothelium and leukocyte migration into the vascular wall and inhibits vascular smooth muscle cell proliferation.[41] Also, formation of isoprostanes
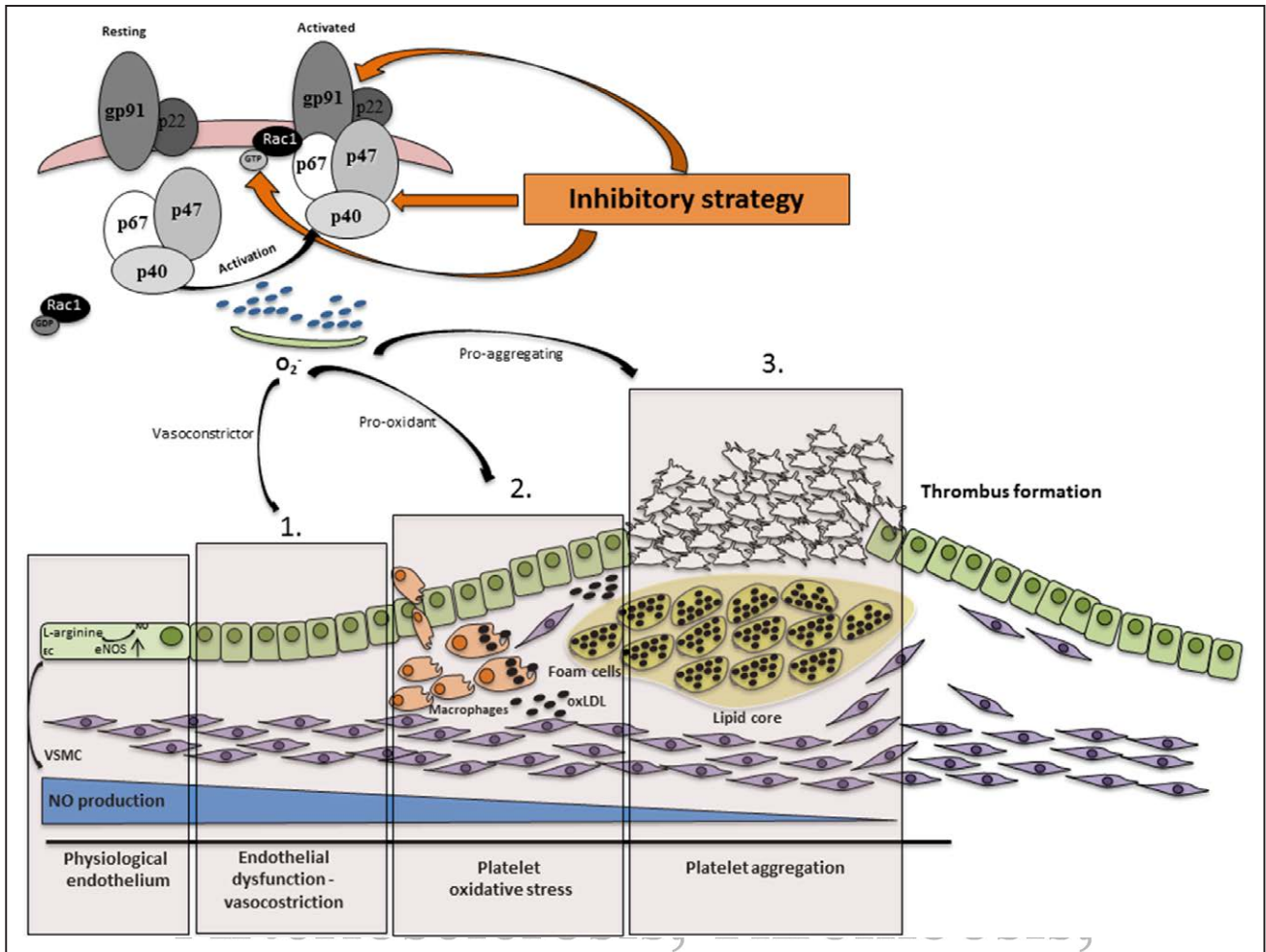
Figure 3. Hypothetical role of NADPH oxidase-2 (Nox2) in the process of atherothrombosis and potential therapeutic strategies. Once generated by the cytosolic subunits Rac1, p40phox, p67phox, and p47phox assembly to the membrane subunits gp91phox/p22phox and resulting O_2^- yields vasoconstriction, low-density lipoprotein (LDL) oxidation, and platelet-related thrombosis. Potential inhibitory strategies include direct inhibition of the Nox2 catalytic core or inhibition of the cytosolic subunits such as Rac1 and p47phox. EC indicates ; and eNOS,

induces mitogenesis of vascular smooth muscle cells, proliferation of fibroblast and endothelial cells, and overexpression of endothelin 1 in mouse aortic endothelial cells.[42] Moreover, thromboxane receptor blockade, with downregulation of isoprostane activity, improves the antiatherogenic effect of thromboxane inhibition in LDL receptor–deficient mice.[43]

Nox2 and Thrombosis: Experimental and Clinical Studies

Several studies consistently demonstrated a key role for ROS in eliciting platelet activation and aggregation.[44,45] Indirect support for the role of Nox2 in platelet aggregation was provided by experiments on human platelets incubated in vitro with antioxidants such as diphenyleneiodonium, apocynin, or a specific Nox2 inhibitor, which inhibited platelet aggregation by downregulating calcium mobilization and GPIIb/IIIa activation.[44] Further studies documented that human platelets express Nox2, and human platelets from patients with Nox2 hereditary deficiency have almost complete absence of superoxide anion formation.[44] Platelet Nox2 is functionally relevant as indicated by ex vivo experiments performed in platelets from healthy subjects. Thus, platelet recruitment

and thrombus growth by blood perfusion at the wall shear rate of 1500 s($^{-1}$), which mimics thrombus growth in vivo, are influenced by ROS and, in particular, by 8-iso-PGF2α,[9] a chemically stable eicosanoid that induces platelet aggregation via thromboxane A$_2$ receptors.[44] Aggregation of platelets obtained from CGD patients was significantly reduced in association with impairment of 8-iso-PGF2α production. Addition of 8-iso-PGF2α or L-NAME improved platelet recruitment in CGD patients, suggesting platelet 8-iso-PGF2α and NO activity/biosynthesis inhibition as 2 potential mechanisms accounting for Nox2 proaggregating property[9] (Figure 2). These data were confirmed by Walsh et al[12] in an ex vivo perfusion analysis of Nox2 knockout mouse where collagen-induced thrombus formation at arterial shear was significantly impaired.

In studies of collagen-induced platelet aggregation, Nox2 was shown to be associated with rapid superoxide anion conversion to H$_2$O$_2$, which activates platelets via intracellular calcium mobilization[46]; catalase, an enzyme that destroys H$_2$O$_2$, inhibited platelet aggregation in this model.[46] Downstream effects of H$_2$O$_2$-induced calcium mobilization include production of thromboxane A$_2$ A$_2$, via arachidonic acid release from

platelet membrane and a thromboxane-independent mechanism occurring via PLC upregulation.[46]

The interplay between Nox2 activation and H_2O_2 production in the process of platelet activation was demonstrated by Dayal et al, who investigated thrombotic events in wild-type C57BL/61 mice or mice overexpressing glutathione peroxidase-1, another enzyme that detoxifies cellular H_2O_2.[47] Mice overexpressing glutathione peroxidase-1 compared with wild-type mice had a longer time to artery occlusion and a lower susceptibility to venous thrombosis.[6] A similar inhibitory effect was observed in mouse control platelets treated with apocynin, indicating that H_2O_2-mediated platelet activation was dependent on Nox2 regulation. Accordingly, H_2O_2 overproduction by platelets was associated with significantly higher levels of mRNA for the catalytic subunit Nox2 and the cytosolic subunit p47[phox] but not for Nox1 and Nox4.[6]

Oxidation of LDL by platelets may represent another mechanism through which Nox2 activates platelets (Figure 2). Thus, in a medium containing LDL, human activated platelets are able to form oxidized LDL, which in turn propagates platelet activation and enhances thrombus size in an ex vivo model of shear-induced thrombosis.[48] Both these effects, that is, LDL oxidation by activated platelets and shear-induced thrombosis growth, were impaired in samples from CGD patients.[48]

The key role of Nox2 in platelet-related thrombosis has been confirmed recently in a mice model of Nox2 deficiency by Delaney et al.[49] Comparing NOX1[(−/y)] and NOX2[(−/−)] knockout mice, the authors found that, although platelet ROS generation was defective in both knockouts, laser-induced arterial thrombosis was impaired in NOX2[(−/−)] but not in NOX1[(−/y)] mice. Wild-type thrombocytopenic mice injected with Nox2[(−/−)] platelets also showed defective arterial thrombosis. Interestingly, bleeding time was not affected in Nox2[(−/−)] mice, suggesting a role for Nox2 in thrombosis but not in hemostasis.[49] This finding is in keeping with our previous report demonstrating that, despite impaired platelet eicosanoid biosynthesis, CGD patients are not at increased risk of bleeding.[9] Platelet Nox2 is also relevant in the process of vascular occlusion occurring in the inflammation-related thrombosis disease; thus, Kim et al[50] demonstrated a key role of Nox2 for platelet–neutrophil interactions during vascular inflammation induced by tumor necrosis factor-α.

Nox2 and Vascular Disease

To study Nox2 activity in CGD patients and in patients at risk of cardiovascular disease, we developed an immunoassay, which measures a portion of Nox2 detectable in the supernatant of agonist-stimulated cells and in serum.[51] Blood analyses of this peptide demonstrated that ≈90% of Nox2 stems from stimulation of leukocytes, lymphocytes/monocyte, and platelets, indicating that this assay reflects prevalently ex vivo Nox2 activation by blood cells.[51] In accordance with this, we found that patients with X-linked CGD had lower blood levels of Nox2 compared with healthy subjects.[51] We also investigated the relationship between Nox2 and cardiovascular disease in cross-sectional and prospective studies. Thus, Nox2 has been shown to be upregulated in patients with several

risk factors, such as hypercholesterolemia, obesity, smoking, hypertension, and diabetes mellitus.[3] Interestingly, an early increase of Nox2 activity has been detected in children affected by hypercholesterolemia[3] and obesity[3] coincidentally with intima–media thickness increase and lowered FMD.[8,16,22]

Prospective study suggested that Nox2 activity might be predictive of cardiovascular diseases. Thus, in 1002 atrial fibrillation patients on treatment with oral anticoagulants,[52] a significantly increased cumulative incidence of fatal and nonfatal cardiovascular events was observed across tertiles for Nox2 activity with a higher incidence of events in patients with elevated Nox2 activity.[52] This study, however, did not prove a cause–effect relationship between Nox2 activation and cardiovascular disease. Randomized controlled trials with Nox2 inhibitors are necessary to demonstrate that such interplays may occur in vivo.

Therapeutic Perspectives and Conclusions

Investigation on CGD patients makes it possible to postulate mechanisms through which Nox2 might be involved in the atherosclerotic and thrombotic processes. Nox2-derived O_2^- is vasoconstrictive and may be implicated in the artery dysfunction in the early phase of atherosclerosis (Figure 3). Later on, Nox2-derived O_2^- could contribute to atherosclerotic plaque via endothelial activation, oxidation of LDL, and its uptake by macrophages[53] and eventually vascular occlusion by eliciting platelet activation and thrombus growth[9] (Figure 3). On the basis of these findings, it would be tempting to suggest Nox2 as a novel target for atherosclerotic disease, but it is a matter of concern whether Nox2 downregulated in humans would have negative effects on the innate immune system. The similar platelet aggregation inhibition detected in X-linked CGD Nox2 carriers versus patients with X-linked CGD suggests that ≤50% Nox2 inhibition is a reasonable therapeutic goal to inhibit platelet function without an increased risk of bleeding. Similarly, X-linked carriers of CGD are not susceptible to increased infection except in settings of extreme lyonization of the X chromosome when ≈5% of the neutrophils are normal.[54] Alternatively, Nox2 downregulation could be achieved via inhibition of its cytosolic subunit p47[phox], which has less negative impact on the innate immune system as indicated by the more favorable clinical history of patients with this hereditary deficiency of the disease.[7] Finally, inhibition of another cytosolic subunit, Rac1, may represent an interesting option as documented by statin treatment, which is associated with Rac1 downregulation and impaired Nox2-derived oxidative stress and platelet activation.[55]

In conclusion, there is a growing body of experimental and clinical evidence to suggest Nox2 as a good potential target to counteract the process of atherothrombosis. Inhibition of Nox2 would have the peculiarity to positively interfering with the thrombotic process without affecting hemostasis. Therefore, interventional studies with Nox2 inhibitors are warranted to assess the clinical validity of this therapeutic approach in patients at risk or with cardiovascular events.

Disclosures

None.

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Highlights

- NADPH oxidase-2 (Nox2) is an enzyme of the innate immune system that contributes to bacteria killing via production of reactive oxygen species.
- Nox2 is present not only in leucocytes but also in platelets and endothelial cells in which it exerts proaggregating and vasoconstrictive activities, respectively.
- Patients with chronic granulomatous disease, which is associated with Nox2 hereditary deficiency, display impaired platelet activation, enhanced artery vasodilation, and lowered atherosclerotic burden. Similar findings have been reported in Nox2 animal knockout.
- Nox2 may represent a novel target for counteracting atherothrombosis.

Arteriosclerosis, Thrombosis, and Vascular Biology

NADPH Oxidase-2 and Atherothrombosis: Insight From Chronic Granulomatous Disease

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